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THE ACTION OF CERTAIN QUARTERNARY AMMONIUM BASES

BY

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THE ACTION OF CERTAIN QUARTERNARY AMMONIUM BASES

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The possession by quarternary ammonium-bases of a "curare" action, originally indicated by Crum-Brown and Fraser,[1] has become one of the commonplaces of pharmacology. From time to time indications of other types of action have appeared. In particular a number of such compounds have been shown to possess an action of the "muscarine" type; muscarine itself, indeed, being in all likelihood a quarternary base. It is to be noted, however, that all the substances, in which this latter action has been described, have three methyl groups attached to the nitrogen atom, the fourth grouping being usually more complex, as in the case of the various choline esters and ethers recently examined by one of us,[2] or the isoamyl- and hexyl- trimethyl-amines examined by Jordan.[3] Jacobj and Hagenberg,[4] however, showed that the tetramethyl ammonium salts have also a muscarine-like action on the frog's heart, and that, in the frog and mammal, they produce an intoxication in which both muscarine and curare effects can be recognized. The corresponding tetraethyl compounds had no such action; they produced muscular tremors in the frog, but neither curare nor muscarine-action could be detected in the mammal.

This curious difference between the actions of the tetramethyl- and tetraethylammonium salts appears again in the recent work

[1] Proc. Roy. Soc. Edinb., vi, p. 556, 1869.
[2] Journ. of Pharm. and Exp. Therap., vi, p. 147, 1914.
[3] Arch. f. exp. Path. u. Pharm., viii, p. 15, 1877.
[4] Arch. f. exp. Path. u. Pharm., xlviii, p. 48, 1902.

of Marshall,[5] whose observations are chiefly concerned with the stoppage of respiration, which is produced in the mammal by intravenous injection of the tetramethyl compounds, and which Marshall attributes to the peripheral curare-like effect on the nerve-endings in voluntary muscles. Incidentally he deals also with the effects on the circulatory system, in which he recognizes a peripheral muscarine-like effect, and a central stimulation of the vasomotor centre. More recently Loevenhart[6] attributes the effects of tetramethylammonium salts on both blood-pressure and respiration to central action.

Having been engaged for some time with observations on the action of various derivatives of choline and formocholine, some of which have been published, we were led to reëxamine the action of tetramethylammonium hydroxide, which may be regarded as the simplest member and parent base of the group: any of the others being derived from it by substitution in one of the four methyl-groups. As described in the earlier paper,[7] we have been led to recognize two different types of action, exhibited with varying absolute and relative intensity by different members of this group of bases—a nicotine and a muscarine action. We propose to show here that these types of action are recognizable in the action of the parent base, tetramethylammonium hydroxide, the nicotine-like action of which is, indeed, extraordinarily powerful; and that they sufficiently account for its action on the circulatory system, and for its various effects on involuntary muscle and gland-cells, without recourse to hypothetical action on the medullary vasomotor centre, etc. We have, further, confirmed the absence of stimulant activity of this type in the case of the corresponding tetraethyl ammonium salts, as previously recorded by one of us,[8] among other observers, and have added an observation which

[5] Trans. Roy. Soc. Edin. l, p. 17, 1913; Phar. Journ., May 3, 1913.
We are indebted to Professor Marshall for the opportunity of seeing in MS. other papers which are now in the press.

[6] Journ. of Pharm. and Exp. Therap., v, p. 515, 1914.

[7] Journ. of Pharm. and Exp. Therap., vi, p. 147, 1914.

[8] Journ. of Physiol., xli, p. 28, 1910.

we regard as having significance, in elucidating the meaning of this curious contrast.

Our observations have been limited to the effects shown by involuntary muscle and gland-cells, the action on the voluntary muscular system having been thoroughly described by earlier and contemporary observers. Most of our experiments have been made on cats, which have always been anaesthetised with chloroform, followed by ether, either throughout the experiment, or until the brain has been completely destroyed.

The compounds used were, for the most part, the tetraalkyl-ammonium iodides, which our colleague, Dr. A. J. Ewins, kindly prepared for us, the identity and purity being guaranteed by analyses and physical constants. A few experiments with the chlorides and nitrates showed that, for the dosage we employed, the nature of the anion was a matter of indifference. The solutions were made up freshly as required, and the dose was in all cases indicated as hydroxide, so that the nature of the salt used made no difference to the dosage. For the sake of brevity the compounds are sometimes referred to as T M and T E. Thus 1 mgm. T M means 1 mgm. of tetramethylammonium hydroxide (usually as iodide).

II. THE ACTION OF TETRAMETHYLAMMONIUM HYDRATE

Action on the circulation

That the action of tetramethylammonium salts, on the circulation of the mammal with intact central nervous system, is complex and variable, is clear from its description by previous observers. Marshall states that, in the anaesthetised mammal, the intravenous injection of tetramethylammonium chloride invariably causes a fall of blood-pressure, partly due to peripheral stimulation of vagal endings, causing a slowing of the heart-beat, and partly to a peripheral vasodilatation. In decerebrate animals, receiving no anaesthetic, he observed a preliminary fall, due to slowing of the heart-beat, a secondary brief rise of pressure, followed by a third more lasting phase of lowered blood-pressure partly due to vasodilatation. The sharp rise of pressure, occur-

ring as the second phase of the action, Marshall attributes to stimulation of the vasomotor centre. The preliminary slowing of the heart-beat, but not the rest of the complex, is abolished by atropine. In a preliminary note, recently published, Loevenhart attributes the circulatory effects, as seen in dogs, to stimulation of the cardioinhibitory and vasomotor centres.

Our own observations on the cat are so far in agreement with those of Marshall, and of Loevenhart, that they clearly indicate

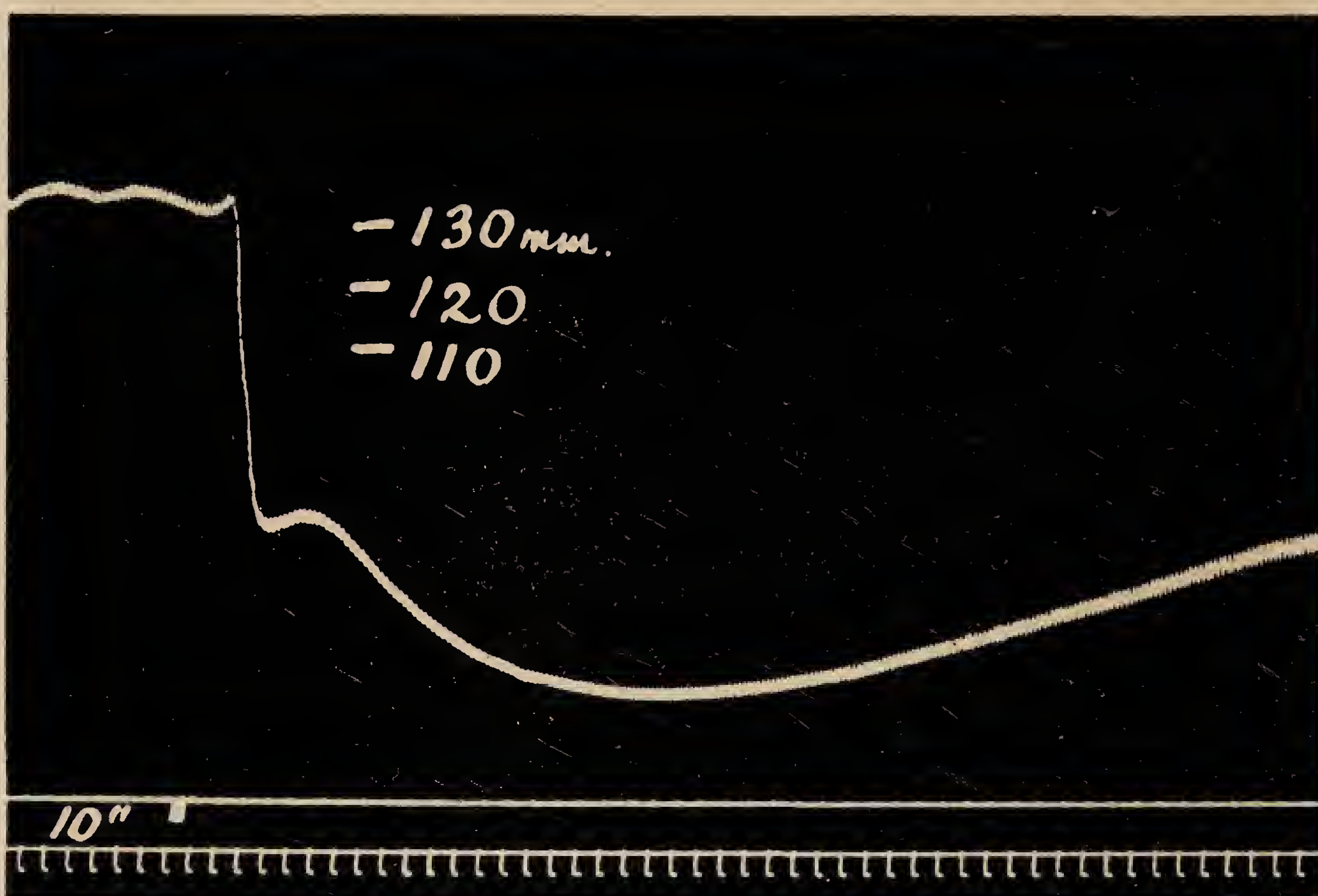

FIG. 1. CAT

Ether. Artificial respiration. Effect on carotid blood-pressure of 1 mgm. T M intravenously.

the existence of two opponent types of action, one tending to raise, the other to lower the blood-pressure, which acquire a varying prominence with varying conditions. It has been our usual, though not invariable experience, to obtain a pure fall of blood-pressure when T M was injected intravenously into a cat under ether. Two stages can be recognised in the fall. In the first stage the pressure falls rapidly, with considerable slowing of the

heart-beat. This effect begins to pass off, so that the pressure remains briefly stationary, or may even begin to return towards the normal, before the second slower and more prolonged fall sets in, during which the heart-beat is no longer slowed, and may even show acceleration slightly beyond the original rate. This, the usual type of effect seen under ether, is strongly reminiscent, in a much weaker form, of the muscarine-like action of cer-

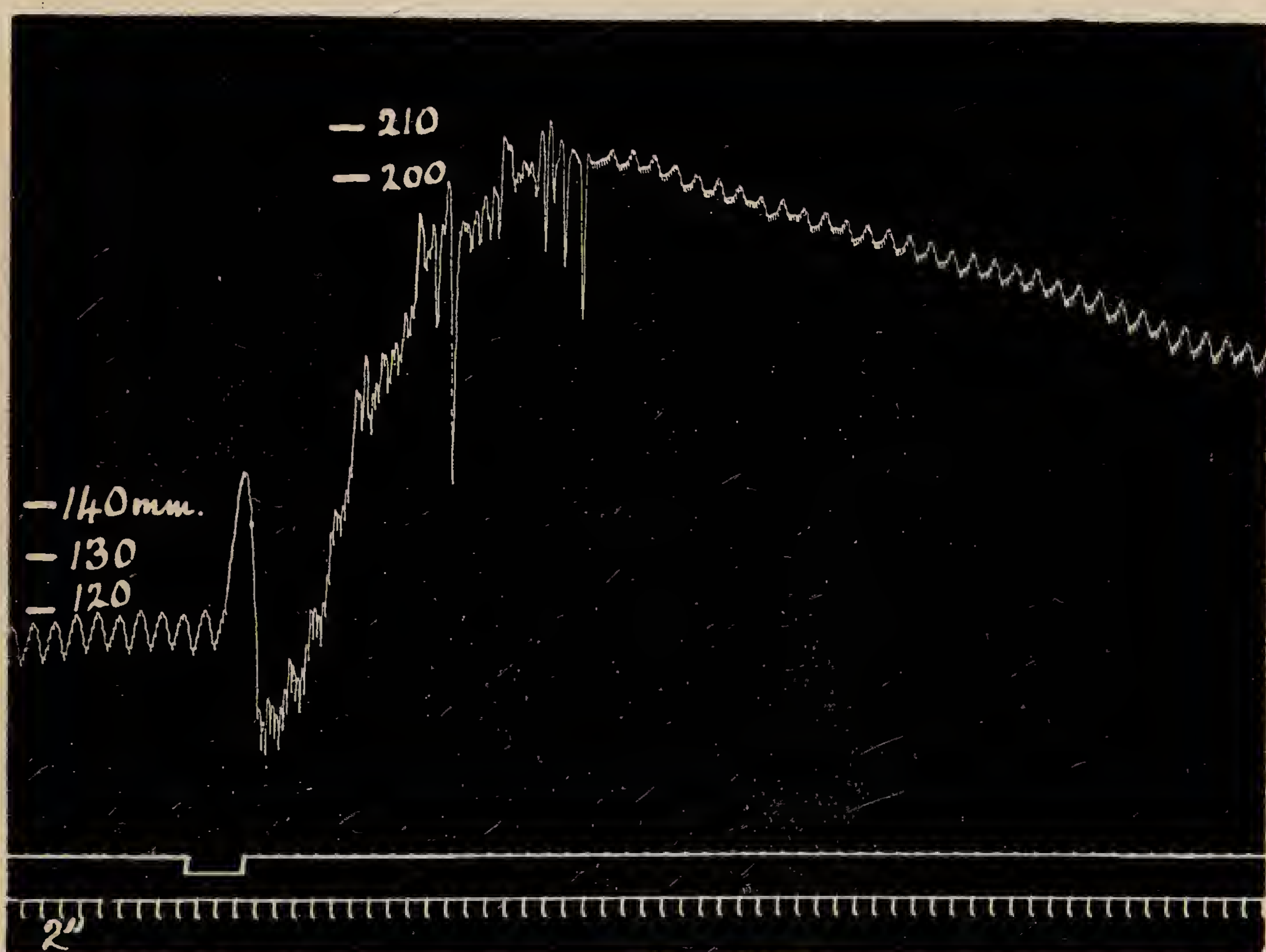

Fig. 2. Cat

Ether. Less usual (mainly pressor) effect on carotid blood-pressure of 1 mgm. T M intravenously.

tain choline-esters, and especially of acetyl-choline, as recently described by one of us. It is illustrated in figure 1. But with T M, even in the non-atropinised cat under ether, and with secondary effects due to respiratory failure excluded by artificial respiration, the main effect on the circulation is occasionally a rise of blood-pressure, even though the heart-beat shows an initial marked inhibition. Figure 2 illustrates this less common, but not

rare effect. We agree with Marshall in finding that the cardiac inhibition is unaffected by section of the vagi, but abolished by atropine (cf. fig. 3); in our experience, however, which on this point differs from that of Marshall, the main effect after atropine, even in the etherised animal, has always been a sharp rise of blood-pressure, though this is usually followed by a slow secondary fall.

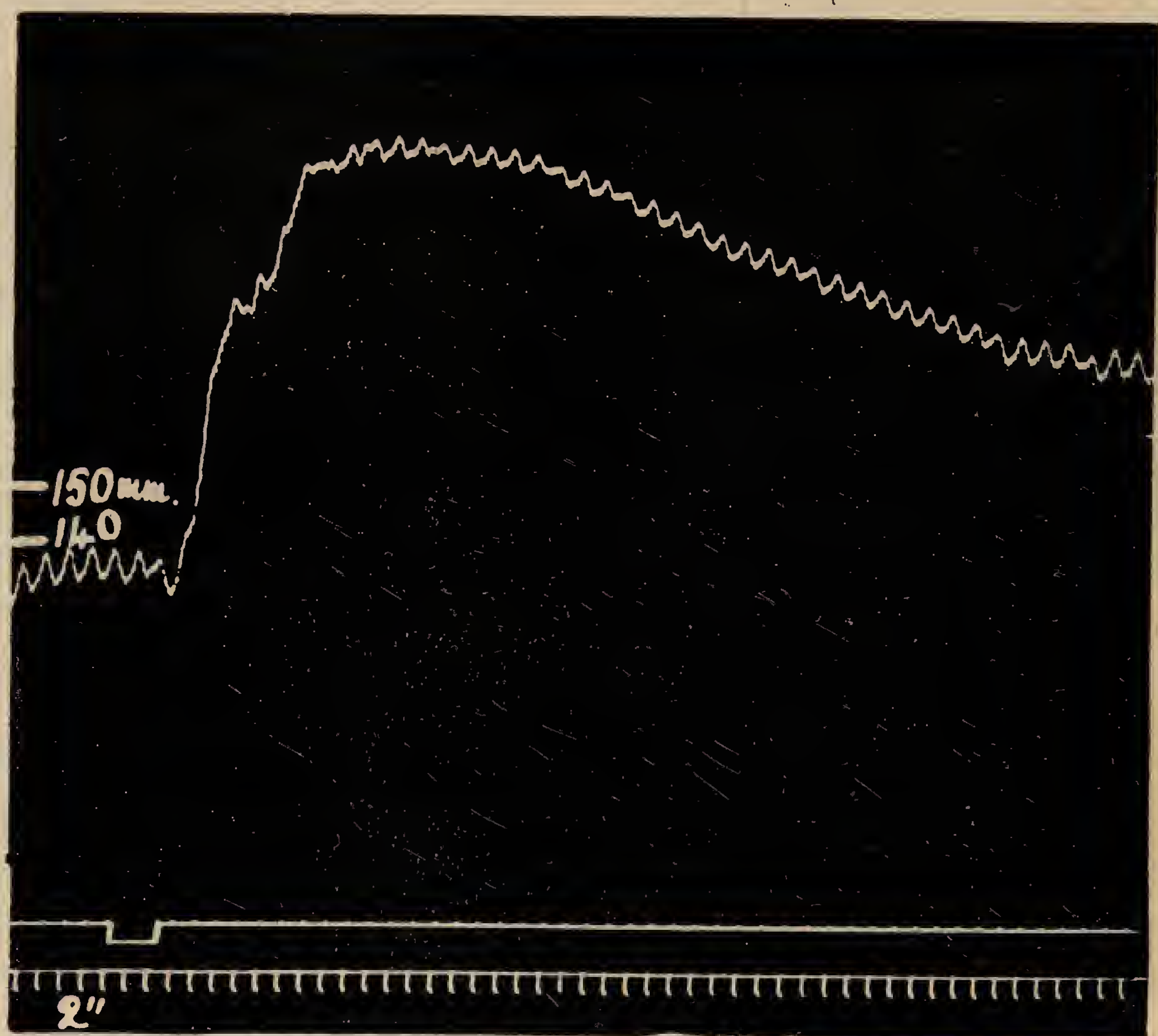

Fig. 3

Same as figure 2. 1 mgm. T M, after 1 mgm. atropine.

This rise of pressure, which Marshall observed only in decerebrate animals, and which he, following Iodlbauer, attributed to action on the vasomotor centre, is certainly not to be so explained. It is seen in most striking form in the cat whose central nervous system has been destroyed completely by pithing. Figure 4 shows the effect, after pithing, on the blood-pressure of the cat which, under ether, produced the tracing shown in figure 1.

In deeply etherised cats the neutral arch of the second vertebra was removed, the cord cut across, the medulla and brain thoroughly stirred up by thrusting a stick through the foramen magnum, and the cord down to the lumbar region similarly destroyed with long, stout steel wire, distally armed with a short, blunt hook. The foramen magnum and neural canal were then firmly plugged with plasticine. Artificial respiration with pure air was applied as soon as the brain was destroyed.

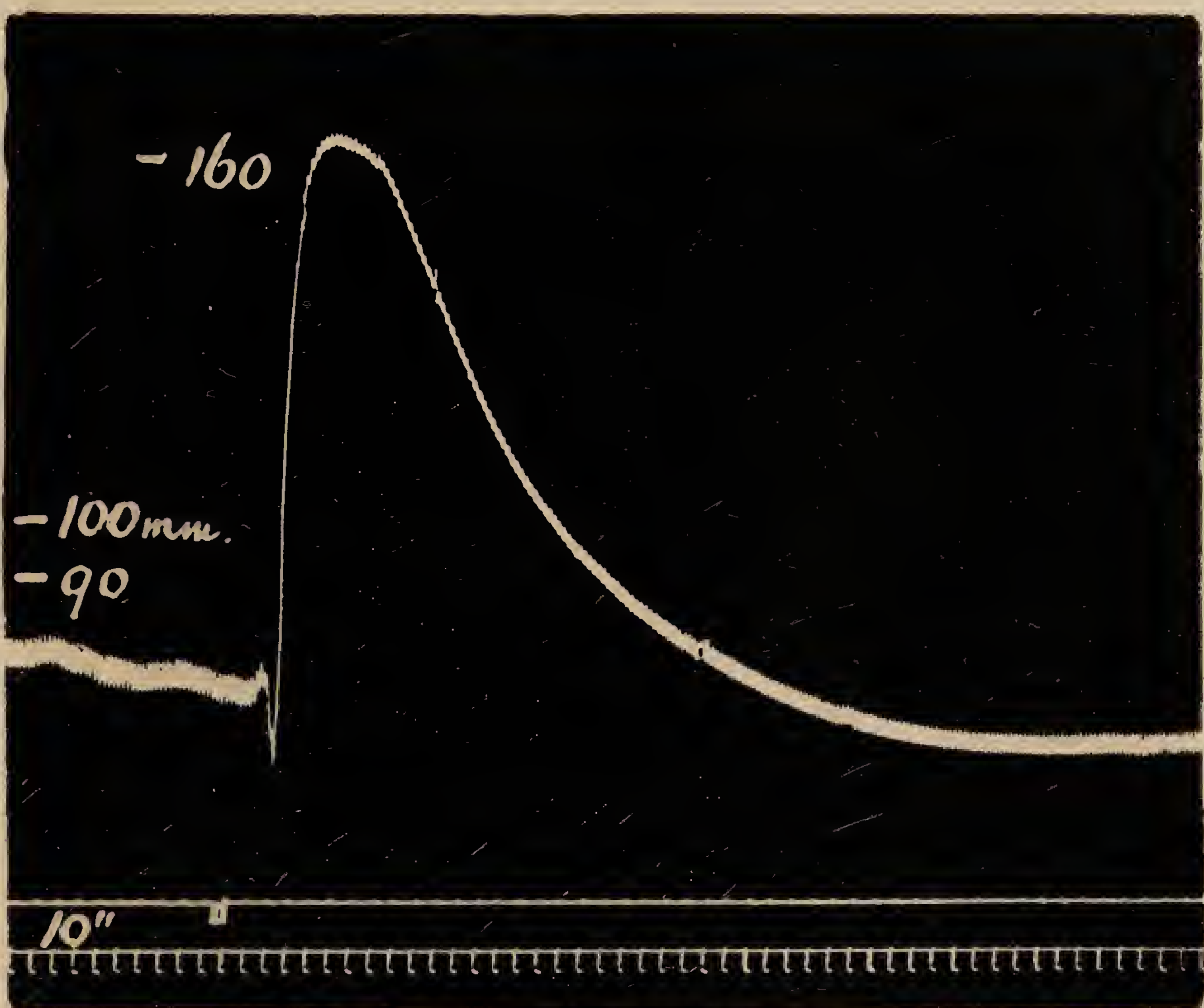

Fig. 4

Same experiment as figure 1. Cat now pithed. Effect of 1 mgm. T M intravenously.

In an animal so prepared, with a low, steady blood-pressure, injection of 0.5 to 1 mgm. T M caused a very brief fall of blood-pressure, due to inhibition of the heart-beat, followed by a relatively enormous rise, with accelerated heart-beat. The whole effect, indeed, is strikingly similar to that produced by a similar dose of nicotine (fig. 5).

In the completely pithed animal, then, we can study the pressor effect in relatively uncomplicated form, and localise it more exactly. By giving a small dose of atropine we eliminate the preliminary cardiac inhibition, and obtain a pure pressor effect, with cardio-acceleration. We have not troubled to make plethysmo-

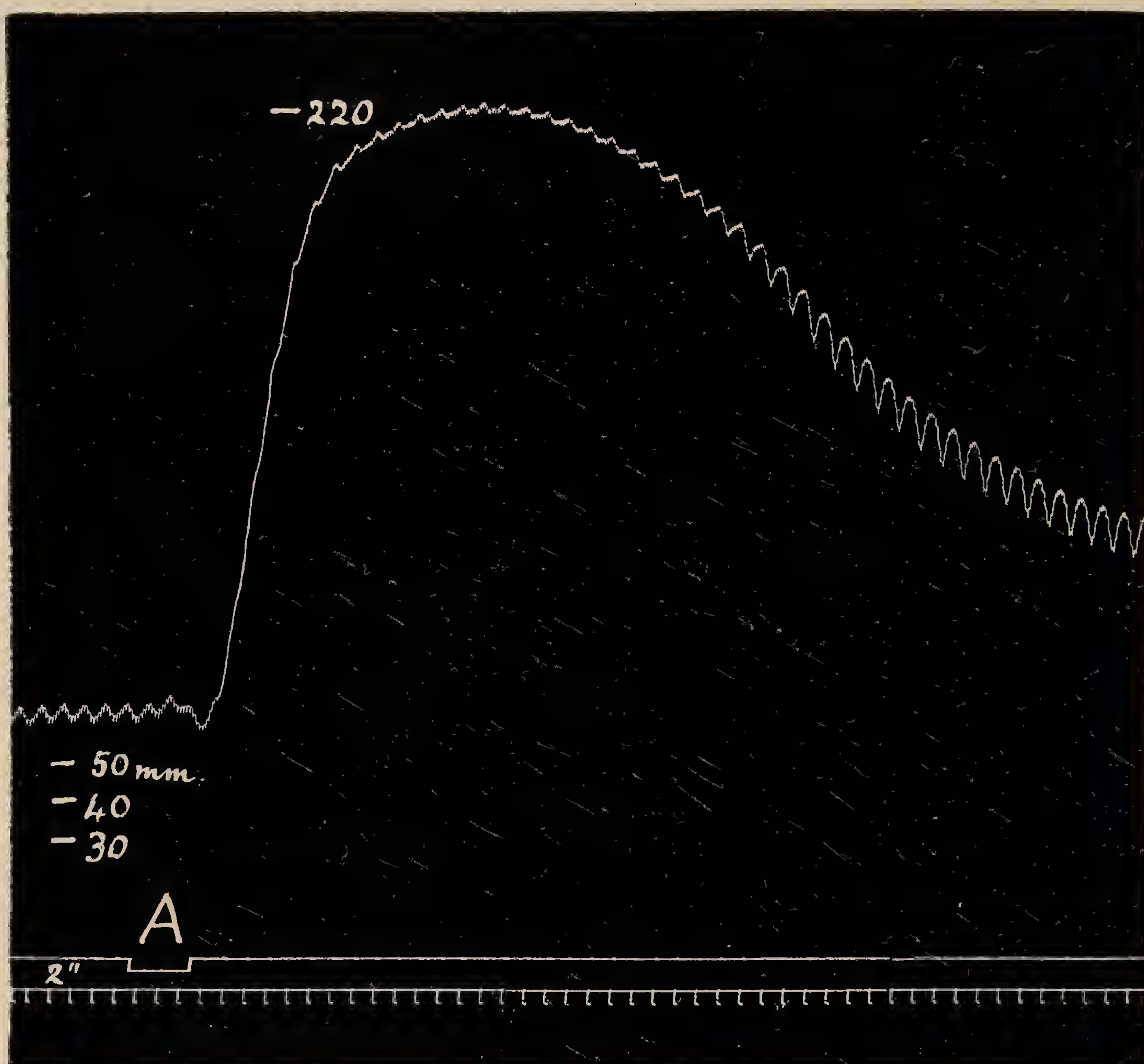

FIG. 5. COMPLETELY PITHED CAT

Artificial respiration. Effect on carotid blood-pressure of 1 mgm. T M intravenously.

graphic records; the rapidity and extent of the pressor action are such as can only be produced by intense general vasoconstriction, with some acceleration of the heart-beat. The central nervous system being eliminated, we have yet to decide whether the vasoconstriction is due to action on the sympathetic ganglion-

cells ("nicotine" action) or on some more peripheral structure. The analogy of the not distantly related choline-derivatives and hordenine methioide[9] suggests that the action may be of the nicotine type. It is easy to show that this suggestion is correct. Administration of 20 to 30 mgms. nicotine tartrate completely annuls the pressor action of T M. (fig. 6B), leaving only a depressor action, which, in turn, is annulled by a small dose of atropine (fig. 6C).

As might be expected, ergotoxine, in sufficient dose, reverses the pressor effect, the characteristic vasodilator fall of pressure

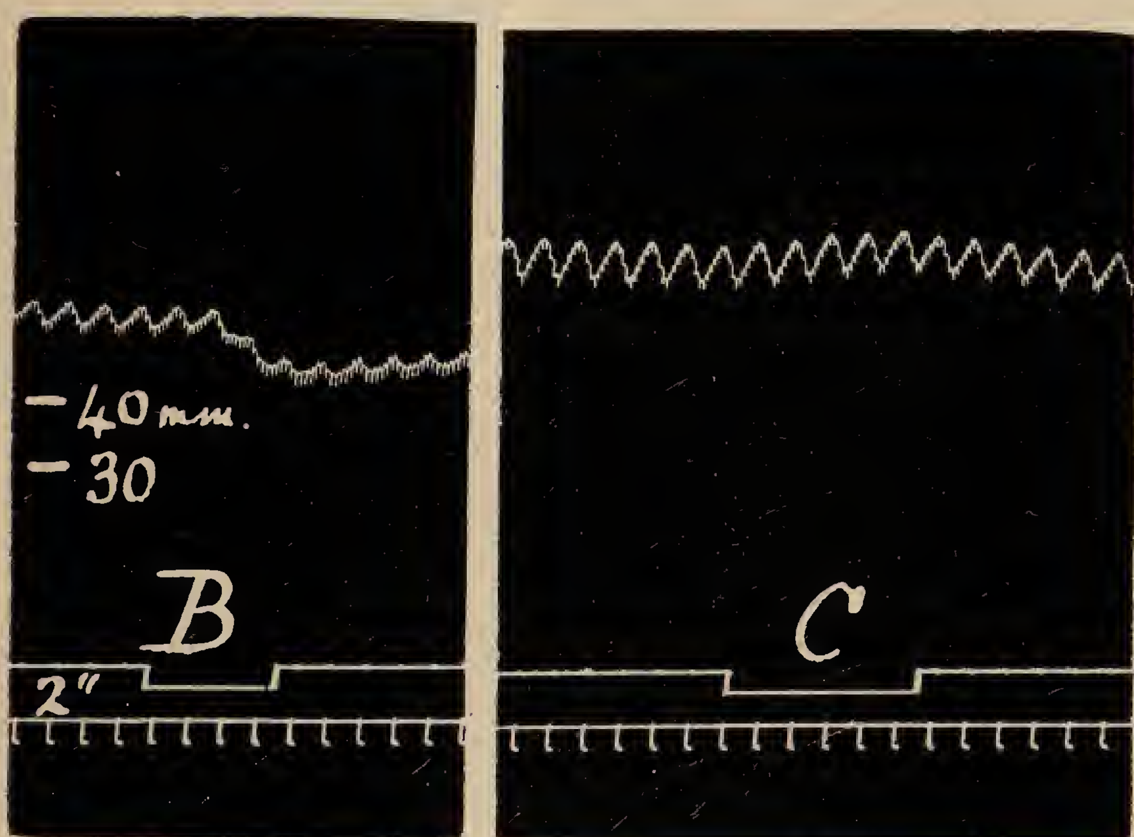

FIG. 6

Continuation of figure 5. Further injections of 1 mgm. T M; *B*, after 30 mgms. nicotine; *C*, after further injection of 1 mgm. atropine.

being produced; but, as in the case of nicotine, a considerably larger dose of ergotoxine (10 mgms. or so for a cat) is needed to produce this reversal, than is needed to reverse the effect of an equipressor dose of adrenine (fig. 7). It seems highly probable that accelerated output of adrenine from the suprarenal medulla plays a part in the pressor action of T M, as in that of

[9] Cf. Dale: Journ. of Pharm. and Exp. Therap., vi., p. 147, 1914; and Barger and Dale: Journ. of Physiol., xli, p. 35, 1910.

nicotine. We have contented ourselves with showing that, after removal of both suprarenals, the rise of pressure is somewhat smaller, but still very large. In any case it may be concluded

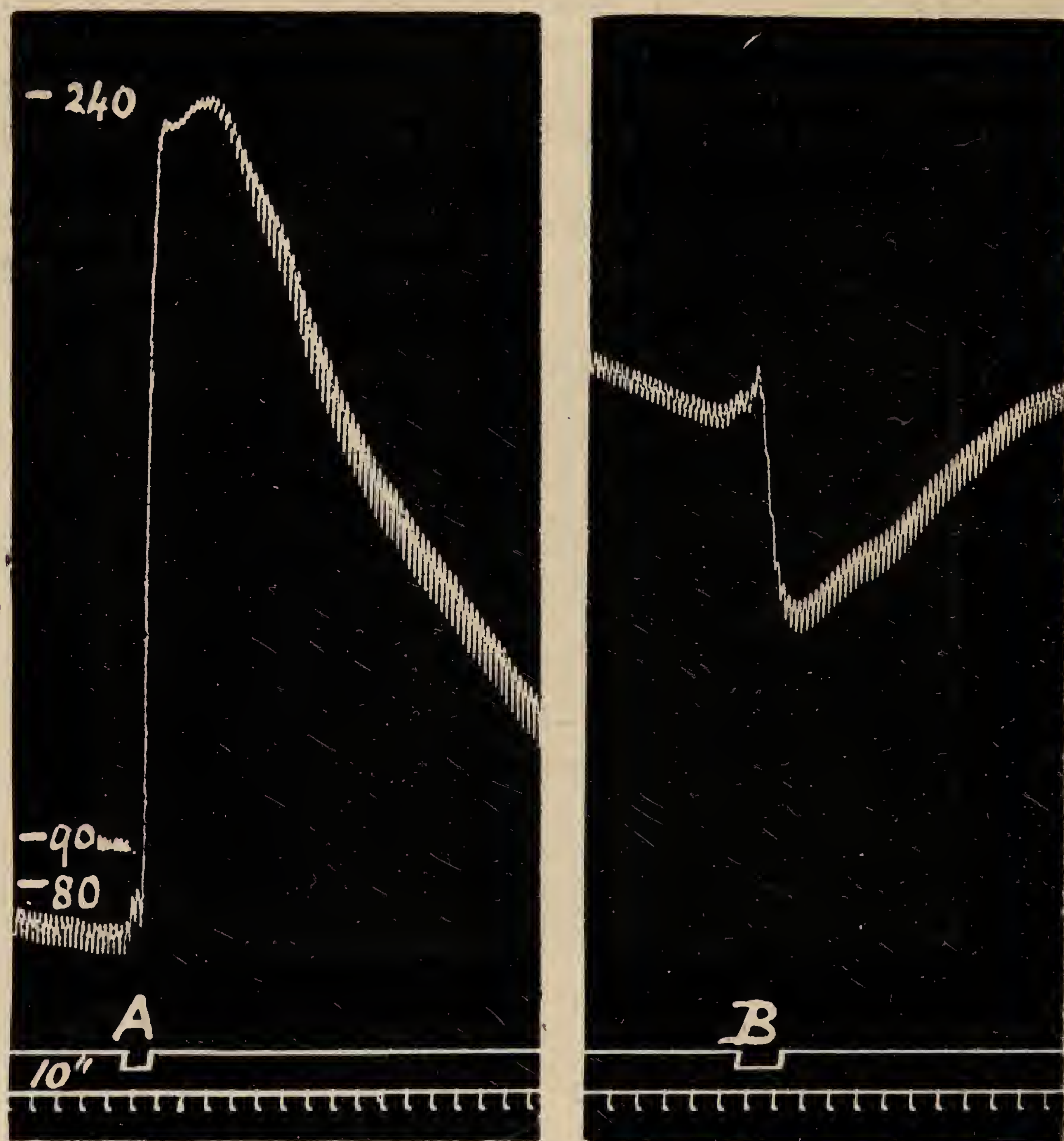

Fig. 7. Completely Pithed Cat

Effects of 1 mgm. T M on carotid blood-pressure; *A*, before, *B*, after injecting 10 mgms. ergotoxine phosphate.

that the rise of blood-pressure is due entirely to action on sympathetic ganglion-cells and on the morphologically equivalent cells of the supra-renal medulla. There is no evidence for stimulation of the vaso-motor centre playing any part in the phenome-

non; while the paralysing effect of nicotine definitely excludes a direct action on structures more peripheral than the ganglion-cells.

The nature of the pressor effect being thus established, we are in a better position to consider the depressor action, and to examine the conditions which determine the predominance of one or the other. In the first place, though individual differences certainly play some part, it is easy to show that, in cases showing a pure depressor effect under anaesthetic, one can obtain a practically pure pressor effect in the same animal after complete pithing of the central nervous system (figs. 1 and 4). It would appear, then, that ether exerts some peripheral as well as a central depressant influence. If we suppose that an anaesthetic of this type so depresses the ganglion-cells, that the more peripheral, inhibitor, muscarine-like action on heart and blood-vessels becomes predominant over the weakened effect of ganglionic stimulation, we obtain a plausible explanation of the contrast between the action on the etherised and pithed animal respectively. This explanation, however, is hardly sufficient; for, in the cat under ether, even when the preliminary muscarine-like action has been eliminated by atropine, the initial pressor effect of T M is generally followed by a longer, and sometimes more considerable fall of pressure. This can only be attributed to the secondary depression of ganglion-cells by the nicotine-like action of the base; for we shall see that T M, like nicotine, paralyses ganglion-cells after stimulating them. We imagine, therefore, that the second, slower phase of the fall of pressure, normally seen under ether (cf. fig. 1), is similarly due to the weakening of tonic impulses from the vasomotor centre by the partial paralysis of ganglion cells.

The action of T M on the cat's blood-pressure may be regarded, then, as a combination of three effects—a peripheral, muscarine-like inhibition, a nicotine-like stimulation of the ganglion cells, and a subsequent depression of the same. Under conditions in which the ganglion-cells are already transmitting tonic impulses from the centre, and at the same time have their responsiveness depressed by anaesthetic, it is easy to see how the muscarine-

like inhibition, and the subsequent blockage of impulses from the vasomotor centre, may become the predominant features of the effect; whereas when the centres are destroyed and anaesthetic removed, and the ganglion-cells are accordingly free from tonic stimuli and, at the same time, highly responsive, the excitatory, nicotine-like effect upon them of a small dose of T M is so powerful as to become the outstanding feature of its action. The contrast produced by varying the conditions is, indeed, the same as that produced, by a similar change, in the apparent effect of choline,[10] but is here seen in an even more striking form.

We have stated that the action of T M on the blood-pressure of the pithed cat is qualitatively very similar to that of nicotine. Quantitatively, also, the resemblance between the two stimulant effects is very close. In its paralytic action on ganglion cells T M seems to be somewhat weaker than nicotine; but 50 mgm., given intravenously to a large pithed cat (see experiment in the next section), reduced the pressor effect of 2 mgm. of nicotine to practically *nil.*

Action on the plain muscle of the eye-ball and orbit

In the action on the pupil and nictitating membrane it is easy to detect, as in the action on the blood-pressure, a primary and relatively weak muscarine-like action followed by a nicotine-like effect. A few seconds after a dose of T M has been injected intravenously a brief constriction of the pupil occurs, accompanied by forward movement of the nictitating membrane. This rapidly gives way to a wide dilatation of the pupil, with withdrawal of the nictitans and opening of the palpebral fissure. This secondary effect can be seen, in the pithed animal, to be coincident in onset with the rise of blood-pressure. As it passes off the nictitating membrane moves far forward over the eyeball, so as to obscure the pupil, as after a dose of nicotine. We have not attempted to discover how much of the dilator effect is due to stimulation of cells in the superior cervical ganglion, how much, as in the case of nicotine, to the secondary effect of acceler-

[10] Cf. Dale: Journ. of Pharm. and Exp. Therap., vi, p. 147, 1914.

ated adrenine output from the suprarenal medulla. That both factors are also here concerned is evident from the fact that painting a solution of T M on the superior cervical ganglion produces the dilator effect, and that, on the other hand, removal of the ganglion does not eliminate the dilator effect of injecting the substance intravenously. After large doses, further injections cause no nicotine-like effect, but only a weak muscarine-action. The following experimental record includes observations of these effects on the eye, and also illustrates the paralytic effect of large doses of T M on the action of nicotine subsequently injected.

Experiment. Cat, 3 kilograms.

2.00 p.m. Chloroform, followed by ether. Tracheotomy. Cord cut at second vertebra and medulla and brain pithed. Artificial respiration with pure warmed air. Cannulae in left carotid artery (to record blood-pressure) and right femoral vein (for injections). Right cervical sympathetic nerve tied, cut and dissected up to the superior cervical ganglion, which was also laid bare.

2.25 p.m. Stimulation of right cervical sympathetic. Secondary coil at 40 cm. distance. Complete dilatation of pupil and retraction of nictitating membrane.

2.28. Paint right superior cervical ganglion with 1 per cent solution of T M in saline. Pupil dilates and nictitating membrane retracts. Effect soon passes off. Ganglion washed with warm saline.

2.30. Injection of 1 mgm. T M intravenously. Pupil constricts, nictitating membrane moves forward and eye turns downwards and inwards; then, as the blood-pressure rise becomes established, the pupil dilates widely and the nictitating membrane is retracted. This again passes off as the blood-pressure falls, and the nictitating membrane moves forward over the eye. Salivation and lachrymation are marked.

2.32. Injection of 2 mgm. T M. Similar effects, with smaller rise of blood-pressure.

2.35. Injection of 5 mgm. T M. The secondary dilatation of the pupil is weak and transient. No rise of blood-pressure, but marked inhibition of the heart-beat. Salivation and lachrymation profuse.

2.45. 10 mgm. T M. Brief retraction of the nictitating membrane is the only "sympathetic" effect on the eye. Blood-pressure falls with cardiac inhibition.

2.50. 20 mgm. T M. Pupil gradually becomes more constricted. No effect on the blood-pressure.

2.55. 15 mgm. T M. Pupil gradually becomes more constricted. No effect on the blood-pressure.

2.57. Stimulation of right cervical sympathetic. Coil at 10 cm. distance. No effect.

3.0. 2 mgm. Nicotine tartrate. No effect on blood-pressure or eyes.

3.2. 5 mgm. Nicotine tartrate. No effect on blood-pressure or eyes.

Effects on other plain muscle

On the cat's intestine, *in vivo,* T M has but a weak and uncertain stimulant action. Under such conditions we should expect to find a conflict between a stimulant (muscarine-like) and inhibi-

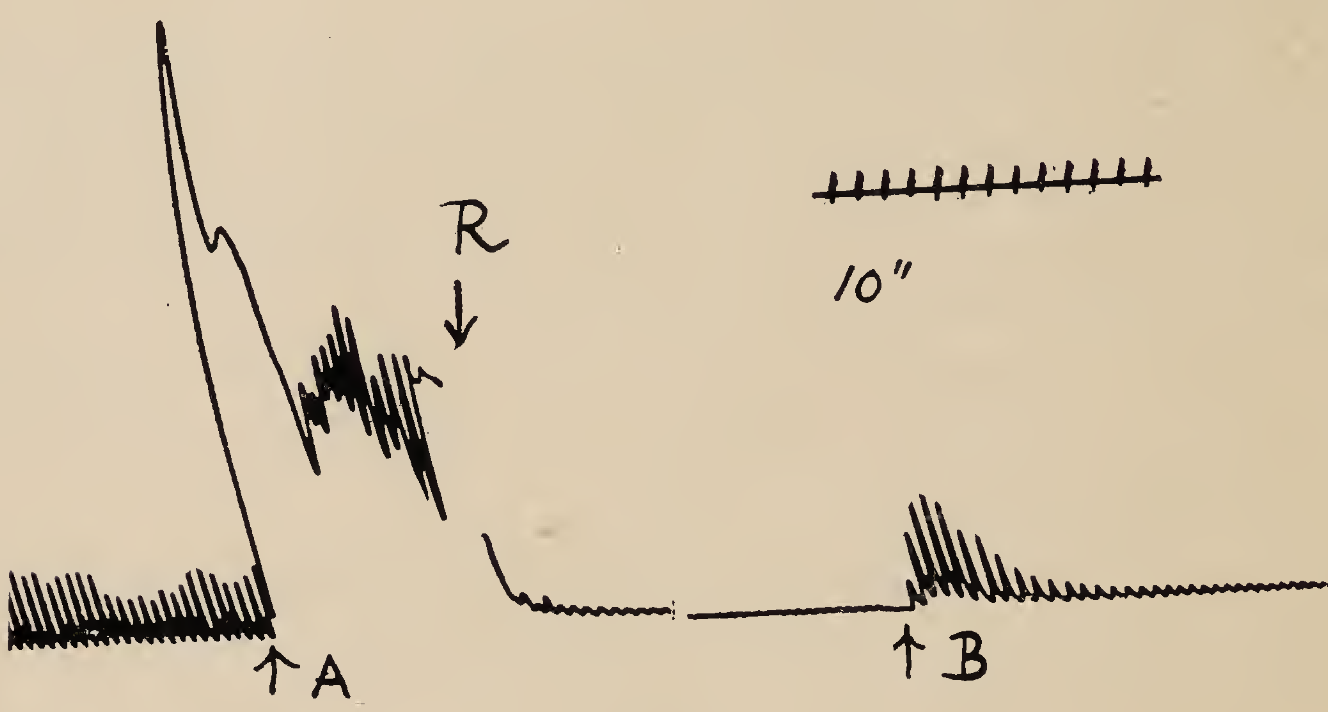

Fig. 8

Loop of rabbit's small intestine, isolated in 50 cc. warm, oxygenated Tyrode's solution. Effects of adding 1 mgm. T M to the bath, *A*, before; *B*, after addition of 0.1 mgm. atropine.

tor (nicotine-like) action. On the isolated intestinal loop of either cat or rabbit a pronounced stimulant action can be observed, but the order of activity is much less than that of muscarine and the choline-esters. Figure 8 shows the effect of 1 in 50,000 T M on a loop of rabbit's intestine. It will be seen that 1 in 500,000 atropine, though it markedly reduces, does not completely abolish the action. On the isolated guinea-pig's uterus, again, tetramethylammonium salts have a not very powerful, but quite decided stimulant action. Figure 9 shows

the effect of 1 in 20,000 T M. This effect on the uterus, like the corresponding effect of muscarine and its allies, is completely abolished by a small dose of atropine.

A few observations were made on the cat's urinary bladder, a volume-record being taken by connecting the bladder by catheter and tubing to a wide reservoir, half full of water, the air-space of which was connected to a Brodie's bellows. The animals were anaesthetised with ether. Injection of 1 to 5 mgms. of T M into a vein caused a contraction of the bladder wall, as the blood-pressure fell, succeeded by a secondary inhibition of tone

Fig. 9

Horn of uterus of virgin guinea-pig, isolated in 50 cc. warm, oxygenated Locke's solution. At *A* added 2.5 mgm. T M.

and rhythm (fig. 10). Atropine reduced, but did not abolish the motor effect.

It may be pointed out that this failure of atropine, to abolish completely the motor effects on the bowel and bladder, is quite

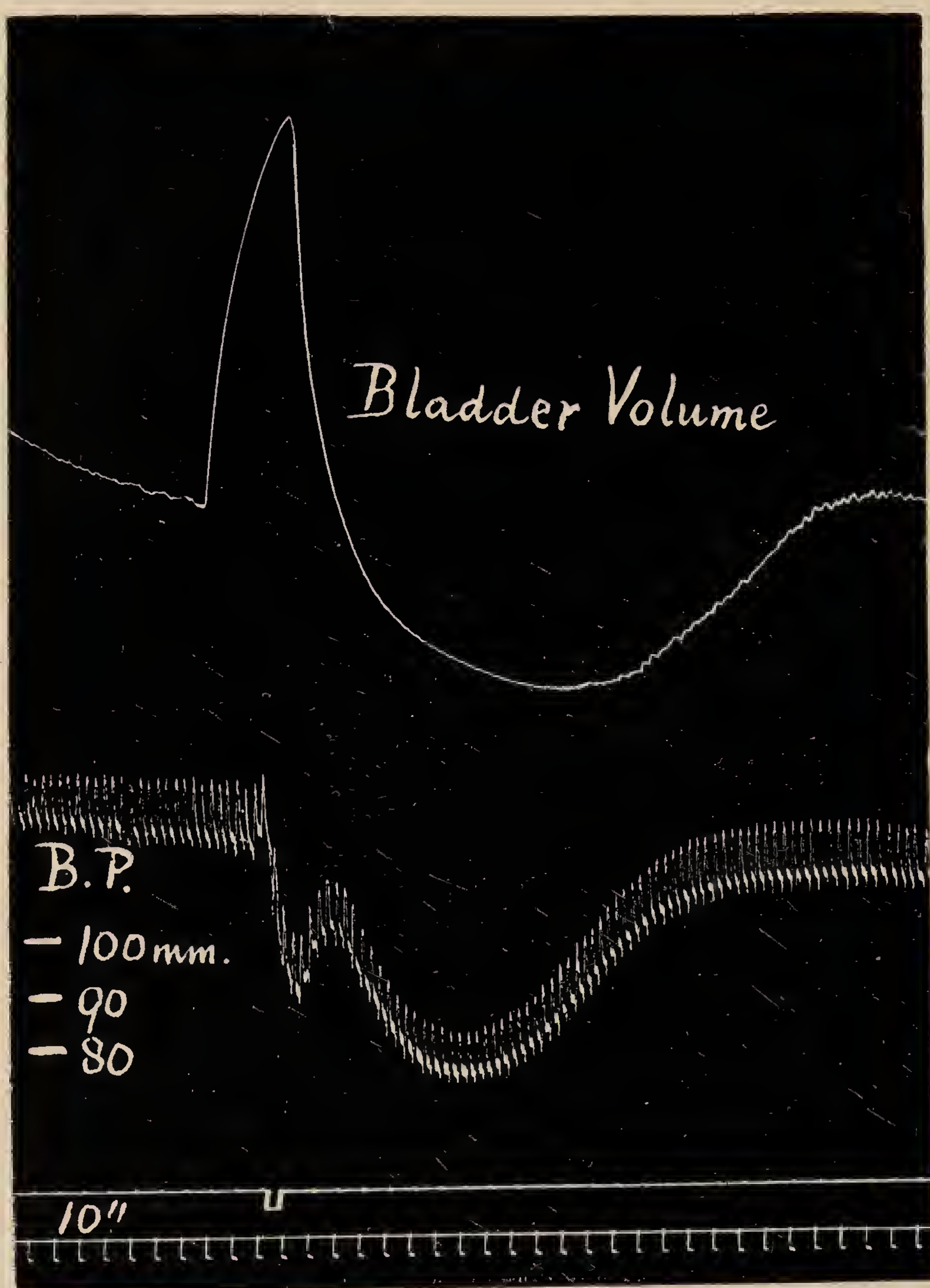

FIG. 10. CAT

Ether. Record of bladder-volume and carotid blood-pressure. Effect of 1 mgm. T M intravenously.

in accordance with the supposition, that they are due in part to a peripheral muscarine-like action, which atropine eliminates, in part to a nicotine-like stimulation of ganglion cells, on which atropine has little effect. It has long been known that atropine

readily abolishes the effects of pilocarpine or muscarine on the intestine and bladder, while it hardly modifies the motor effect on the same structures of impulses in the vagus or pelvic nerves.

Effects on gland-cells

We have already mentioned the lachrymation and salivation which result from intravenous injection of T M. The effect on the salivary flow is not altered by section of the chorda tympani. Doses of nicotine, sufficient to paralyse all ganglion cells, hardly affect it; while a small dose of atropine abolishes the effect immediately. The salivary secretion is, therefore, due almost entirely to peripheral, muscarine-like action.

III. ACTION OF TETRAETHYLAMMONIUM HYDRATE (T E)

The relative inactivity of tetraethylammonium salts, as compared with the corresponding tetramethyl-compounds has, as mentioned in the introduction, been noted by several observers. Jordan found that it had no muscarine-like action, and this was confirmed by Jacobj and Hagenberg. Marshall has also found no evidence of muscarine-like action, and has worked out in detail the difference between the effects of T E and of T M on the voluntary muscles. Our own concern was chiefly with the nicotine-like effect on the blood-pressure of the pithed cat, since this characteristic effect of T M had not previously been recognized. One of us had previously tested T E on the blood-pressure of the pithed cat and found it without action in any ordinary dosage.[11] This inactivity we have confirmed. In a pithed cat giving a very large rise of blood-pressure with 0.5 mgm. T M, T E in doses up to 10 mgm. has no definite action (figs. 11 and 13). Nor have we observed any perceptible stimulant action on any of the organs containing plain muscle or gland cells, the response of which to T M was described in the previous section.

While, however, the stimulant action of T M is lacking in T E, the paralytic action on ganglion cells, though less pronounced,

[11] Journ. of Physiol., xli, p. 28, 1910.

is quite well marked. Figure 12 shows the effect of 0.5 mgm. T M, after injection of 50 mgm. T E. The dose which, as shown in figure 11, previously produced a large rise of pressure, now produces only a fall; while even 5 mgm. T M, though its pressor effect is not extinguished, produces a weaker effect than that which one-tenth of the dose evoked in the unpoisoned animal.

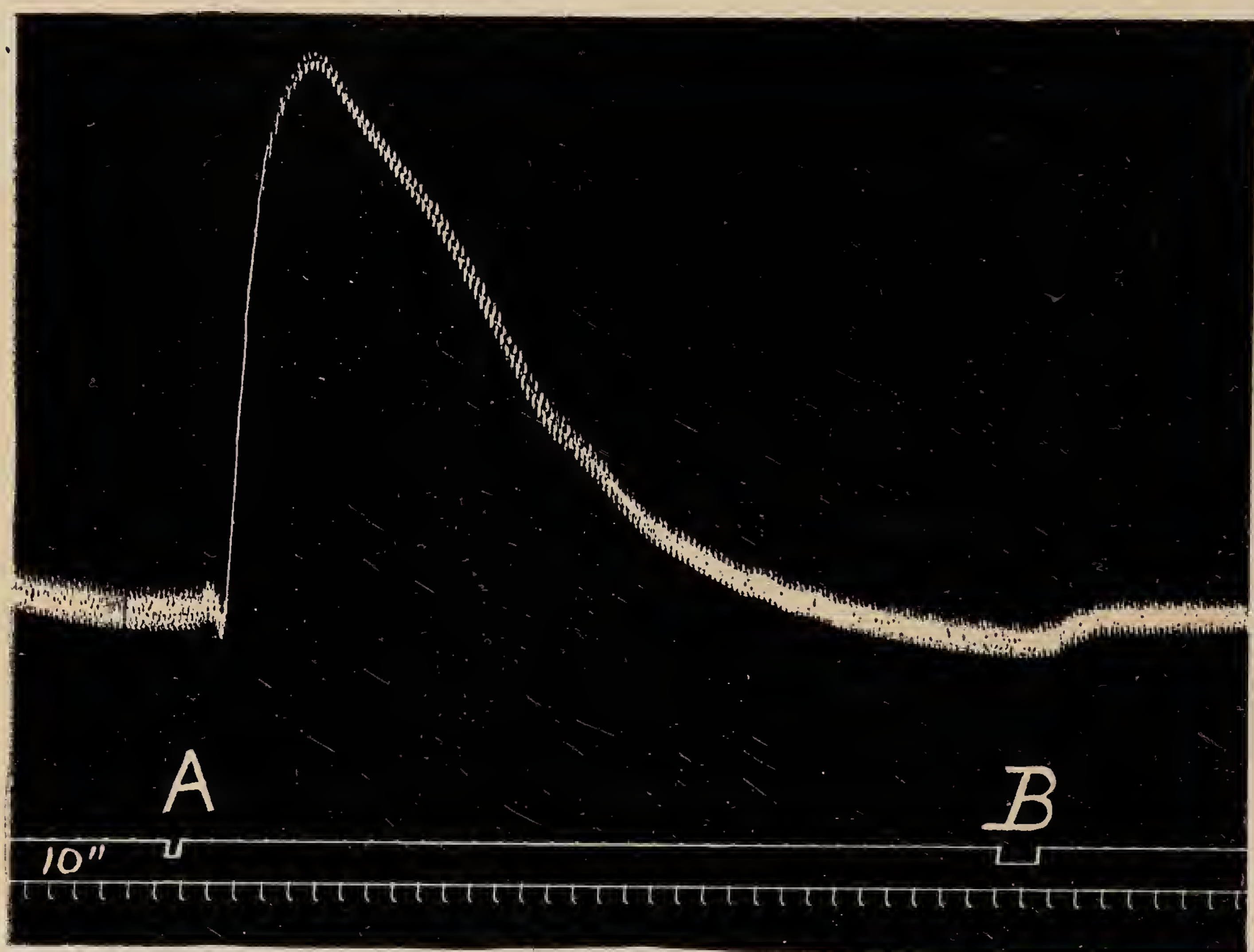

Fig. 11. Pithed Cat

Carotid blood-pressure. *A*, 0.5 mgm. T M; B, 10 mgm. T E.

Of intermediate compounds we have tested only trimethylethylammonium hydroxide, on account of its close relation to choline, and have experimented only with its effect on the blood-pressure. In general it may be said to resemble the tetramethyl-compound in action, but to be only about one-half as active. Figure 13 shows a comparison of the effects, on the blood-pressure of a pithed cat, of trimethylethyl-, tetra methyl-, and tetraethylammonium iodides.

Marshall[12] records that the other intermediate compounds (dimethyl-diethyl-, and methyl-triethylammonium chlorides) "occupy an intermediate position, but they do not exhibit a uniform increase in pharmacological activity with increase of methyl groups."

DISCUSSION AND SUMMARY

These observations bring the action of tetramethylammonium hydrate on involuntary and gland cells into line with that of the different trimethylalkylammonium derivatives which were con-

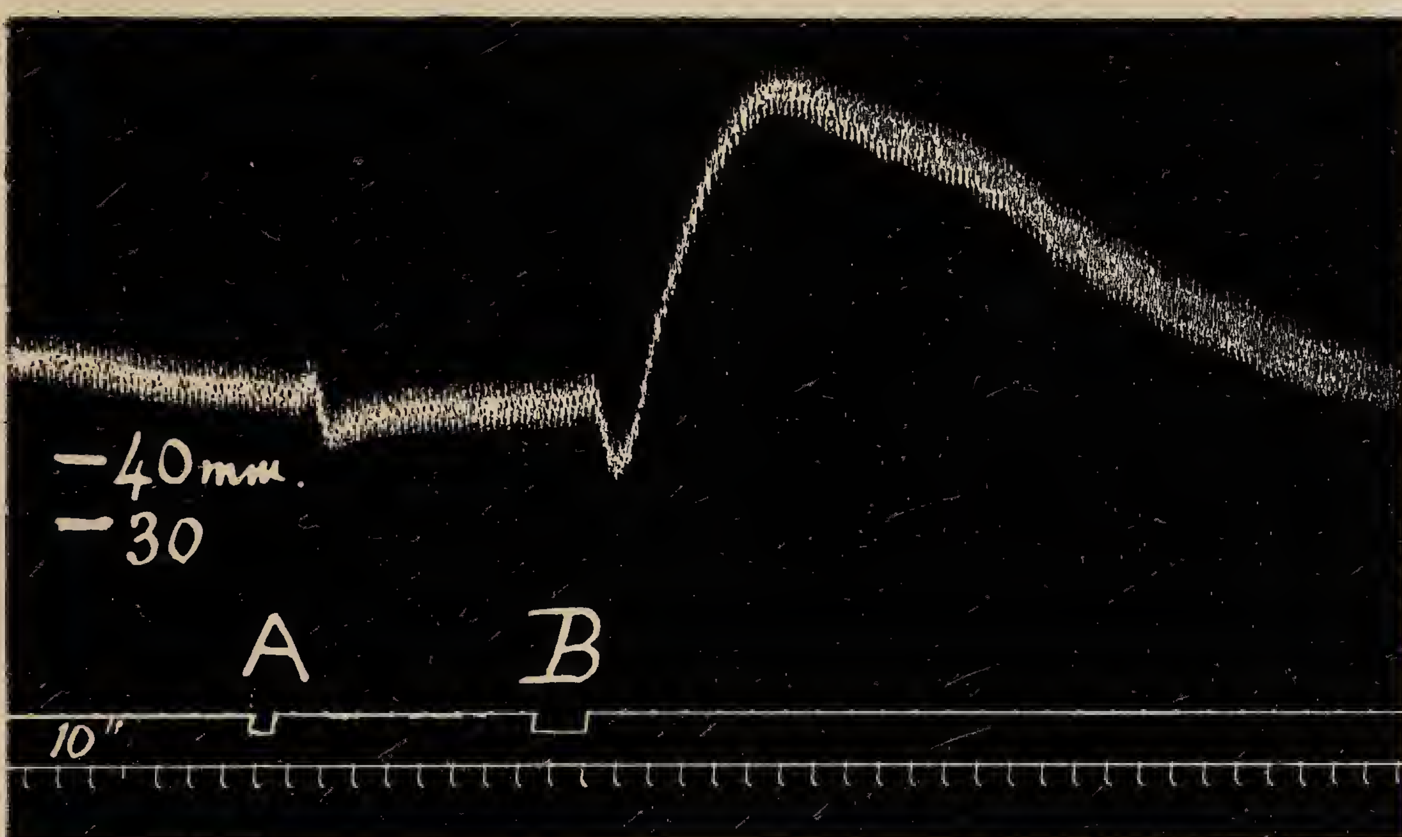

FIG. 12

Same as figure 11. After further injections of T E, amounting to 50 mgm. in all. *A*, 0.5 mgm. T M; *B*, 5 mgm. T M.

sidered in an earlier paper. It was there pointed out that there seems to be some biochemical affinity between the ganglion-cells of the whole involuntary nervous system, and the peripheral terminations of the extra-sympathetic portion of the system; so that a series of substances exists possessing, in varying degrees of absolute and relative intensity, actions of the "nicotine" and "muscarine" types. Tetramethylammonium hydrate, which may

[12] Phar. Journ., May 3, 1913.

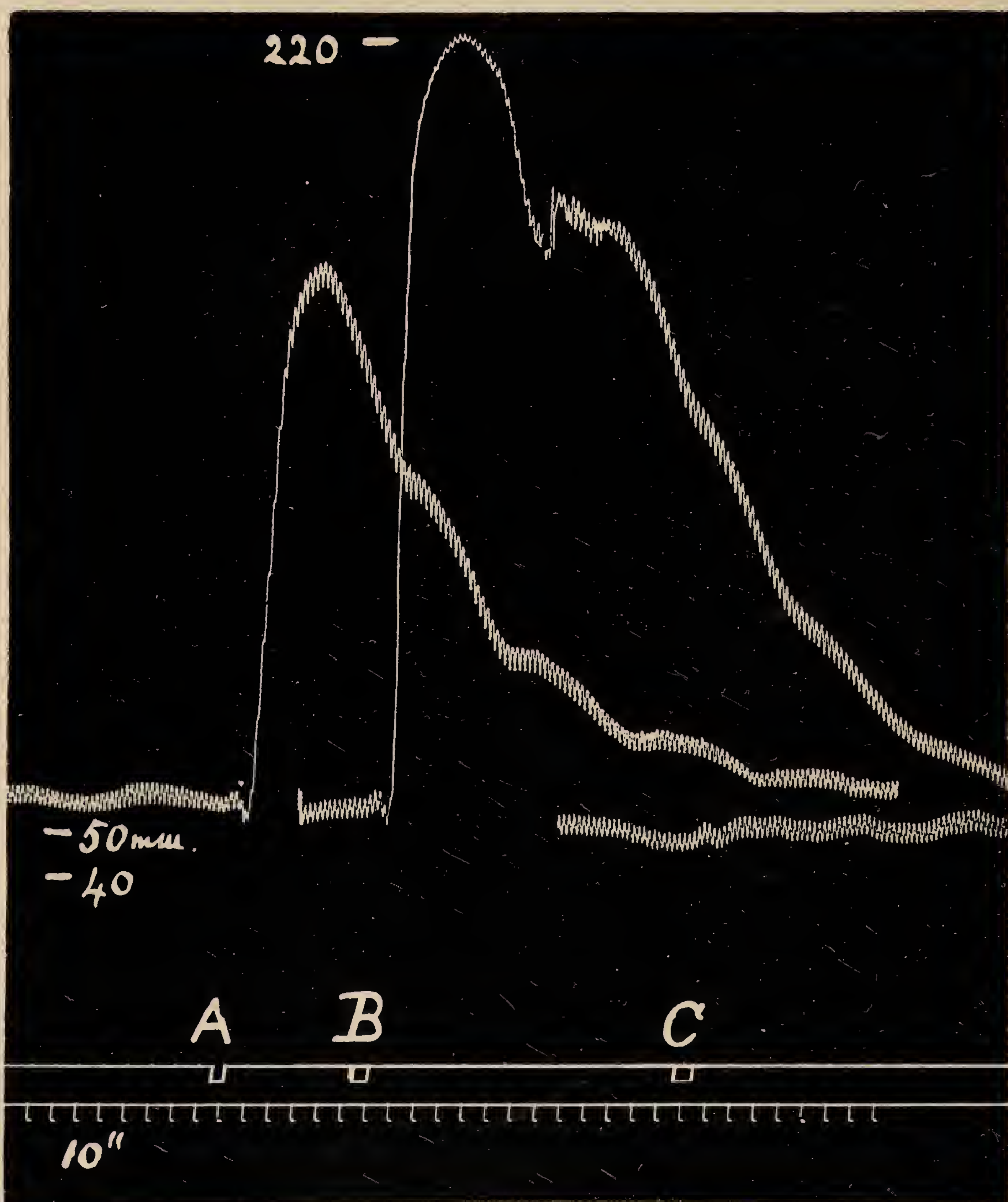

FIG. 13. PITHED CAT

Carotid blood-pressure. *A*, 0.5 mgm. dimethyl-ethyl ammonium hydroxide (as iodide); *B*, 0.5 mgm. T M; *C*, 1 mgm. T E.

be regarded as the simplest member of the series, possesses the nicotine-like action in a very intense degree, being approximately as active in its stimulation of ganglion cells as nicotine itself; it also possesses a weaker, but well-marked action of the muscarine-type.

Neither type of stimulant action on involuntary muscle or gland cells is exhibited by the corresponding tetraethylammonium base. In relation to the peripheral structures associated with the cranio-sacral autonomic endings it appears to be quite indifferent; it neither stimulates itself nor appreciably alters their responsiveness to the tetramethyl-base. On the ganglion-cells, on the other hand, though the tetraethyl-compound has no appreciable stimulating action in ordinary dosage, it exhibits the secondary, paralytic phase of the nicotine-action almost as powerfully as the tetramethyl-compound.

We come back, then, as in every pharmacological investigation, to the ultimate problem of the relation between structure and action; and it appears to us, that the curious contrast between the action of these remarkably similar substances defines the problem with unusual clearness. Here there can be no question of "toxophore" and "haptophore" groupings. We are dealing with substances so simple that in their chemical properties they approach more nearly to the inorganic kations than to the complex alkaloids. The most we could hope would be to attribute the paralytic action on ganglion-cells to some property, common to both, which fixes them to those cells; while the stimulant action must be due to some property in which tetramethylammonium hydrate differs from tetraethylammonium hydrate, but resembles, not only its more or less immediate derivatives, the choline esters, but, even more closely, substances so remote from it chemically as nicotine, lobeline, and cytisine. If such a property of difference and resemblance could be found, its discovery would undoubtedly have a significance extending far beyond the immediate problem of the contrast between these bases. There is good reason, however, for regarding such discovery as improbable. For, if we turn to the action on other structures than those with which our own experiments deal, the

contrast is of a different kind. From the experiments of Jacobj and Hagenberg, and the more detailed investigation of Marshall, it appears that the tetramethyl base has little stimulant effect on frog's skeletal muscle, when injected into that animal; its main effect is a curare-like paralysis, which, moreover, prevents the vigorous fibrillary contractions which the tetraethyl-base normally produces. The difference for which we must look, therefore, is not in some simple physical property, which we could reasonably expect to detect *in vitro;* it is essentially a difference in relation to the specific constitution of an excitable structure. The problem, in other words, becomes physiological rather than pharmacological. Until knowledge is available which suffices to explain the physiological differences between simple inorganic kations, it seems unlikely that we shall arrive at any satisfactory explanation of the differences in physiological action between these relatively simple organic kations, which show an analogous similarity of chemical properties. Nor, while the discrepancy in action between these simple substances remains unexplained, can any satisfactory theory be based on the study of more complex alkaloids.